

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
1 July 2004 (01.07.2004)

PCT

(10) International Publication Number
WO 2004/055515 A1

(51) International Patent Classification⁷: **G01N 33/49, 33/487, 27/76**

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/EP2002/014251

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date:
13 December 2002 (13.12.2002)

Published:
— with international search report

(25) Filing Language:
English

(26) Publication Language:
English

(71) Applicant and

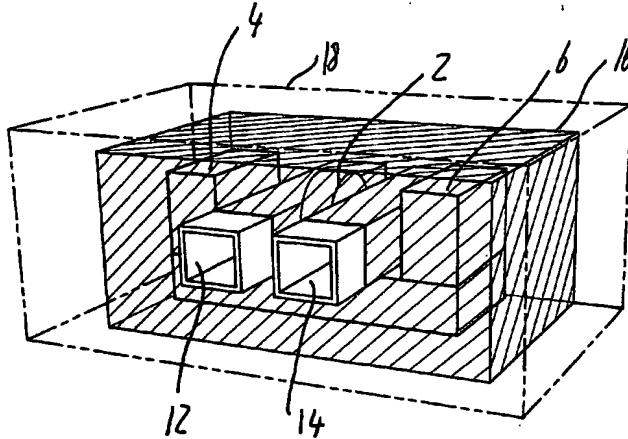
(72) Inventor: **MARINELLI, Mauro** [IT/IT]; Via Razeto 2/1, I-16132 Genova (IT).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(74) Agent: **KARAGHIOSOFF, Giorgio, A.**; Studio Karaghiostoff & Frizzi S.a.s., Via Pecorile, 25/C, I-17015 Celle Ligure (IT).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

(54) Title: SUSCEPTOMETER FOR NON-INVASIVE IRON LEVEL MEASUREMENT IN A BODY



WO 2004/055515 A1

(57) Abstract: A susceptometer for non-invasive determination of iron concentration in a body, by detecting the magnetic flux variation produced by the body. The susceptometer comprises a heat insulating case (16), containing a support structure that defines a screening region (8, 10). The structure supports an alternating magnetic field source, which is able to generate a magnetic field in the screening region, and at least two magnetic field sensors (4, 6), disposed in front of the field source (2). Means (12, 14) for introducing the body to be measured in the screening region (8, 10), temperature-control means, for stabilizing temperature inside the case, so as to limit relative variation to a predetermined maximum value, and means for processing electric signals indicative of the variation in the magnetic field linked to the sensor, which variation is caused by the screened body, in the screening region, are further provided.

Susceptometer for non-invasive iron level measurement
in a body

5 This invention relates to a susceptometer for non-invasive iron level measurement in a body, and particularly to a susceptometer which is adapted to determine iron concentration by detecting the magnetic field variation produced by the body.

10 A particular and advantageous application of the inventive susceptometer is non-invasive measurement of iron stores in the body of thalassemic patients.

15 Cooley's anemia (also known as beta-thalassemia major or thalassemia major) is a genetic hemolytic disease, resulting from a defective synthesis of hemoglobin. Individuals who suffer from this disease must undergo frequent blood transfusions in order to survive.

20 Since there is no natural way for the human body to eliminate iron, all iron contained in transfused red blood cells builds up and becomes toxic for tissues and organs. Any excess iron removal treatment requires the knowledge of iron concentration. At present, the most reliable method to quantify iron overload is chemical analysis of liver biopsy samples. The concentration of iron in the liver of a healthy individual is of a few hundreds of micrograms per cubic centimeter of wet tissue, and in ill persons it can even reach tens of milligrams per cubic centimeter. None of prior art 25 30 non-invasive methods (concentration of serum ferritin,

urinalysis after the administration of a chelating agent) is sufficiently accurate.

Several methods have been explored to make this measurement in a non-invasive manner and the most 5 promising one seems to be biosusceptometry. At present, three susceptometers exists, in Hamburg (Germany), Cleveland (USA) and Turin (Italy). These apparatuses generate the magnetizing field by using a superconducting coil and read the field variations 10 produced by the presence of the patient, by means of a superconducting gradiometer, connected to a SQUID. The magnetizing coil and the pick-up coil, both fitted on a quartz cylinder are at about the same position relative to the patient. Due to this geometry, the signal is 15 highly dependent from the magnetic properties of the most superficial tissues. Also, the mechanical restrictions of cryogenic apparatuses do not practically allow to provide a suitable geometry for measuring iron overload in internal body parts.

20 An experimental instrument is known (IEEE Transactions on Biomedical Engineering, October 1967, p. 239), for room temperature iron level determination in a body, which substantially comprises a transformer that is cut in such a manner as to create a gap, 25 wherein a body is positioned to be screened.

An improvement of this instrument is also known (Medical & Biological Engineering & Computing, 1980, Vol. 18, p. 253), which comprises thermal shields, designed to insulate the transformer from the heat 30 radiated by the body being screened, and a cooling

system to remove the heat accumulated on said thermal shields.

The above instruments include a measuring circuit, comprising a field source and a sensor, which is 5 designed to transmit a signal derived from the presence of the body in the screening region, and a reference circuit, comprising a field source and a sensor independent from those of the measuring circuit, which is designed to transmit a reference signal.

10 The document Medical & Biological Engineering & Computing further describes an apparatus, in which the transformer is replaced by a solenoid structure. This structure includes an outer primary winding, for generating a uniform magnetic field inside it, an inner 15 measuring secondary winding and an inner reference secondary measurement, the two secondary windings being coaxial with the primary and symmetric with respect to a transverse median plane of the solenoid. The measuring winding is designed to detect a variation in 20 the linked magnetic flux, caused by the presence of a body in the screening region that is internal with respect to said winding, whereas the reference winding provides a reference signal.

In all the above equipment, measurement results 25 are derived from the difference between the signal generated by the screened body and the reference signal.

Nevertheless, these room temperature instruments cannot reach such a sensitivity as to allow in vivo 30 quantification of iron overload in a body.

Particularly, thermal expansion of the apparatus, which is caused by the presence of a body in the relevant area, perturb the measurement signal and the test signal to different extents, thereby causing an 5 additional signal degradation deriving from the difference therebetween.

According to the invention, this problem is solved thanks to a susceptometer in which the measuring sensor and the reference sensor receive signals generated by 10 the same field source, and in which temperature control is further provided to reduce any structural deformation which might change the shape or position of a sensor relative to another or to the field source, thereby reducing the possibility of a difference of 15 spurious signals for the measuring sensor and the reference sensor.

Therefore, the object of the invention is a susceptometer as mentioned hereinbefore, characterized in that it comprises:

- 20 - a heat insulating case, containing a support structure, which is made of a non-magnetic and electrically insulating material, and operationally kept substantially at room temperature, and which defines a screening region;
- 25 - an alternating magnetic field source, supported by said structure and able to generate a magnetic field in said screening region;
- at least two magnetic field sensors (pick-up coils), supported by said structure and disposed in 30 front of said field source;

- means for introducing the body to be screened in the screening region defined by said field source and at least one of said at least two sensors;

5 - temperature control means, for stabilizing temperature inside said case, at least during measurement, in such a manner as to limit relative variation to a predetermined maximum value, so that thermal expansion of the support structure and the associated field source and sensors are substantially 10 ininfluent on the magnetic field flux linked with said at least two sensors; and

15 - means for processing electric signals indicative of the variation in the magnetic flux linked with said at least two sensors, which variation is caused by the presence of the body being screened, in the screening region.

Several embodiments and further improvements of the invention will form the subject of the subclaims.

Further advantages and characteristics of the 20 inventive susceptometer will be apparent from the following detailed description, referred to the accompanying drawings, which are provided as non-limiting examples, in which:

25 - Fig. 1 is a perspective schematic view of an apparatus according to the invention;

- Fig. 2 is a perspective schematic view of the arrangement of the magnet and sensors of the apparatus as shown in Fig. 1;

30 - Fig. 3 is a diagram showing the values of a quantity related with the geometry of the magnet and

sensors of the apparatus as shown in Figure 1;

- Figs 4.-5-6 are diagrams showing the results of measurements performed with the help of a prototype of the inventive susceptometer;

5 - Fig. 7 is a perspective schematic view of the arrangement of the magnet and sensors of an improved embodiment of the inventive apparatus;

10 - Figs. 8 to 11 are different views of a structure for supporting the magnetic field source and the field sensing pick-ups, which is particularly suitable for analyses on human beings;

15 - Fig. 12 is an exploded perspective view of the support structure and the two shell covers thereof for generating a diathermic liquid flow designed to stabilize the temperature of the support structure;

20 - Figs. 13 and 14 are two views of a patient table and the susceptometer as shown in the preceding Figures 8 to 12, with the table in the two different patient insertion positions, i.e. between the lower pick-up and the central magnetic field source and between the upper pick-up and the central magnetic field source.

25 - Fig. 15 is a view taken from the table end side of the table and susceptometer assembly as shown in Fig. 14.

30 - Fig. 16 is a schematic view of a variant embodiment of the combination of a magnetic field source and the pick-ups, in which all the other construction parts have been omitted.

The following description is referred to a prototype of a susceptometer according to the

invention, for measuring relatively small samples, and of a large susceptometer, for measuring iron stores in the body of a human being.

The construction principle is based on the following considerations. Molar susceptibility of iron in ferritin-hemosiderin (iron stores being found in the form of these molecules) is of $+8.2 \cdot 10^{-8} \text{ m}^3 \text{ mole}$. For instance, an iron overload of 0.6 mg/g in an organ reduces the diamagnetic susceptibility thereof by 10%; this iron concentration adds a paramagnetic contribution of $+0.9 \cdot 10^{-6}$ to the susceptibility of a normal organ, which is similar to that of water (the susceptibility by unit of volume in the international system is nondimensional: in the same units, diamagnetic susceptibility of water is of $-9.0 \cdot 10^{-6}$). One of the methods to determine magnetic susceptibility of a body is introducing it in a magnetic field and measuring the field variation caused by the body; for instance, the magnetic field in the proximity of a spherical (diamagnetic) water sample is about 9 parts per million smaller than the uniform magnetic field applied to the sample. In order to measure relevant iron concentrations which, as mentioned above, produce susceptibility variations of the order of one tenth of water susceptibility, the susceptometer shall be able to detect magnetic field variations of at least one part per 10 millions. Relative magnetic field variation ($\Delta B/B$) in the proximity of a weakly magnetic sample introduced in a uniform exciting field is proportional to the magnetic susceptibility of the sample. As is

apparent, the proportionality of susceptibility to relative field variation allowed to give up the high absolute sensitivity of SQUIDs and to provide an apparatus with no low-temperature devices.

5 As shown in Figs. 1 and 2, the susceptometer comprises a magnetic field source 2, e.g. formed by a magnetizing coil adapted to generate an alternating magnetic field. Numerals 4 and 6 denote the two sensors (pick-up coils), disposed symmetrically with respect to
10 the magnetic field source 2.

The field source 2 and the pick-up coils 4, 6 are mounted on an electrically insulating and weakly magnetic support. While the support structure of the Figure is made of plates, supports may be also provided
15 that have a lighter structure, e.g. a tubular shape. The sensitivity of the apparatus is mainly limited by the mechanical stability of this structure, i.e. of spurious magnetic flux variations in pick-up coils, caused by deformations of the structure and/or by the
20 geometry of the magnet and the pick-up coils.

Two screening regions 8, 10 are defined between the magnetic field source 2 and the transducers 4, 6: in order to make measurements, the sample is introduced in one of the two regions and heat-insulated from the
25 apparatus by means of two insulating, non-magnetic tunnels 12, 14.

The apparatus further has a first insulating casing 16, which encloses the support structure and has apertures for sample receiving tunnels. Preferably, the
30 casing 16 is in turn enclosed in a second insulating

case 18. Both cases 16, 18 are made of a weakly magnetic material.

The apparatus further has temperature control means (not shown), which are designed to stabilize 5 temperature inside the casing 16, so that, at least during measurements, the thermal expansion of the structure supporting the associated magnetic field source 2 and the sensors 4, 6 are substantially non-influent on the variation in the magnetic flux linked 10 with the sensors. These temperature control means may include a plurality of non-magnetic heating elements, associated to the support; to this end, carbon resistors may be used, of the type known as Allen Bradley resistors.

15 Temperature control means further include temperature sensors for measuring the temperature of the support in the proximity of each heating element and a feedback control system, to keep the measured temperature constant to a few thousandths of degree.

20 Preferably, the control means also include one or more heating/cooling elements, associated to the walls of the case 16 or 18 or both, which are designed to control the temperature of the environment around the enclosure 16. For instance, coils with a diathermic 25 fluid, like cold water, flowing therein, may be embedded in the walls of the case 18. Here again, the diathermic fluid flow will be controlled as a function of the temperature detected by temperature sensors. Thermal control is further refined, by also associating 30 temperature control means to the walls of tunnels 12

and 14, so that - once a hot sample is introduced therein - those control means are activated to prevent any undesired temperature perturbation.

Finally, the apparatus has means for processing 5 electric signals indicative of the variation in the magnetic flux linked with the sensor, which variation is caused by the presence of the screened body. Those processing means include a lock-in amplifier, which reads the difference between the signals detected by 10 the sensors 4 and 6. The arrangement and connection of sensors is such that, when no sample is inserted, the signal read by the lock-in amplifier is null.

During screening operations, the sample is moved in and out of the screening region (either the region 8 15 or the region 10) several times, each insertion of the sample producing a dominant flux variation in the sensor (pick-up coil) adjacent to the sample (sensor 4 for the screening region 8 and sensor 6 for the screening region 10). A computer records the signal, in 20 synchronism with the insertion and exit of the sample; this additional synchronous detection allows measurement to be independent from the little drift that is still present, in spite of the above described temperature control. Equation 1 below is used to 25 determine the contribution to the magnetic field flux, linked with the pick-up coil, due to the presence of the sample:

$$\phi = \frac{-}{\mu_0} \int_{Volume} \chi(r) B \cdot b \cdot dr \quad (1)$$

where μ_0 is vacuum magnetic permeability, $\chi(r)$ is

the magnetic susceptibility of the material, B is the exciting magnetic field and b is the magnetic field which would be generated by the pick-up if a unit current flew across it; the integral is calculated on 5 the sample volume.

Referring now to Figure 3, the two-dimensional diagram a) shows, in a gray scale, the values of the inner product ($B \cdot b$), related with the magnet-sensor geometry, in the region between the exciting magnet and 10 one sensor: darker areas denote a positive inner product and a higher intensity, brighter areas denote a decreasing intensity until the inner product reaches negative values. It may be noted that this inner product is generally not uniform in space, and varies 15 in terms of both intensity and sign. As is apparent from equation 1, the magnetic field, hence the sensitivity of the instrument, depends from the product ($B \cdot b$). The region of space (hereafter sensitivity region), in which this product is substantially other 20 than zero, has the shape of a cylinder which is coaxial with the field and in one specific embodiment, has a diameter of about 6 cm and a volume of 200 ml. In diagram b), the inner product ($B \cdot b$) is shown as a function of the position x on the axis of symmetry of 25 the magnetic field. In diagram c), the inner product ($B \cdot b$) is shown as a function of the radial position y on an axis equidistant from the magnet and the sensor.

Figure 4 shows the signal produced by the repeated insertion and extraction of a 170 cc water sample, 30 contained in a plastic container, in and from the



apparatus. It shall be noted that, in this specific embodiment, the contribution of a water sample, integrally contained in this region, to the signal, is of -30nV/g , whereas the contribution of a sample 5 outside the region is substantially null. The water sample signal increases with the sample volume. The magnetic field in the sensitivity region is no higher than a few tens of Gauss and oscillates at a frequency of a few hundreds of Hz.

10 Once the signal per unit of volume produced by the above water sample (-30nV/g) and the susceptibility of ferritin-hemosiderin ($+8.2 \cdot 10^{-8} \text{ m}^3 \text{ mole}$) are known, 1 mg of iron (ferritin-hemosiderin) container in the sensitivity region may be determined to produce a 15 signal of 4.9 nV. Due to the 25nV noise affecting the measurement, the minimum amount of iron (ferritin-hemosiderin) inside the sensitivity region, detectable by the susceptometer is of 5 mg. This means that average iron concentration measuring sensitivity in a 20 sample, whose volume occupies the whole sensitivity region (200 cc for this susceptometer), is of 0.025mg/ml. For instance, in a water sample of 170 g, the sensitivity of the apparatus allows to detect a susceptibility variation of 0.5%, which is equivalent 25 to an iron concentration variation of 0.030 mg/g (see Fig. 4). Iron concentration measuring sensitivity worsens as the sample volume decreases.

An instrumental noise of 25nV is about 3 parts per 10^8 of the signal at the ends of each sensor. It shall 30 be noted that, in order to detect relative field

variations below one part per 10^7 , relative variations in the susceptometer size, during the measuring step, shall be of the same order of magnitude or lower: the susceptometer of the invention allows to reach this

5 result.

With reference to the diagrams of Figures 5 and 6, it may be noted that the spatial inhomogeneity of the inner product ($B \cdot b$) allows to obtain different signals depending on the location of a sample relative to the

10 sensitivity region. In fact, the diagrams of these figures show the curve of the signal detected by the apparatus as a function of the sample position in the screening region with reference to a neutral axis (0 position), corresponding to the median axis of the

15 region, relative to a sample with an inhomogeneous arrangement of iron ions. The sample is contained in a prismatic plastic case, having a volume of about 410 cc. In diagram of Figure 5: curve a) is related to a demineralized water sample; curves b), c) and d) are

20 related to the signal generated by samples that contain, inside the main casing, a second case with 16 cc of an iron ion solution with a concentration of about $3000 \mu\text{g}_{\text{Fe}}/\text{cc}$; in the three curves b), c) and d), the secondary case is positioned in different regions

25 of the main case, to create a sample with an inhomogeneous iron distribution. In the diagram of Figure 6: curve a) is related to a demineralized water sample; curve b) is related to the signal generated by a sample that contains, inside the main casing, a

30 second case with 16 cc of an iron ion solution with a

concentration of about $3000\mu\text{g}_{\text{Fe}}/\text{cc}$; and curve c) is related to the signal generated by a sample that contains, inside the main casing, two cylindrical cases, each containing about 16 cc of an iron ion solution with a concentration of about $3000\mu\text{g}_{\text{Fe}}/\text{cc}$.

Figs. 5 and 6 clearly show that this specific embodiment of the apparatus has a spatial resolution of about 2 cm, i.e. it may resolve iron accumulations at a distance of more than 2 cm from each other.

In accordance with an improved embodiment, which is shown in Fig. 7, in the proximity of the field source 2 two additional sensors 20, 22 are mounted in symmetrical positions with respect to the source 2. The additional sensors 20, 22 are disposed in such a manner that the variation in the magnetic field fluxes linked therewith, caused by the presence of a body in the sensitivity region, is substantially a function of the magnetic properties of the outermost areas of this body only. Hence, the measuring configuration of Fig. 7 allows to determine the magnetic properties of the inner region of the sample, by subtracting, with an appropriate weight, the signal produced by the sensors 20, 22, from the signal produced by the sensors 4, 6.

An advantageous embodiment of the susceptometer as shown in the preceding Figures 1 to 7 also has, alternatively to or in combination with the foamed tunnels 12 and 14, a gap for feeding a flow of diathermic liquid, particularly water, at a controlled temperature. In fact, the heat given to the apparatus by the screened body, which is accommodated in the

foamed tubular chambers, was found to have a detectable effect, which causes a signal drift, due to infinitesimal variations of the structure supporting the magnetic field generator and the magnetic field 5 sensors.

The diathermic temperature-controlled liquid flow removes the heat generated and introduced in the susceptometer structure by the body being screened.

An additional variant consists in removing both 10 the foamed tubular members, and the casing 16 of the embodiment described with reference to Figure 1.

Here, the susceptometer structure is housed in a case whose shape corresponds to the structure of the assembly composed of the supporting members, the 15 magnetic field source and the magnetic field sensing pick-ups and the case has a two-shell conformation, in which a liquid-tight gap is formed, having at least one feed inlet and one drain outlet, to obtain a diathermic fluid flow, which surrounds at least the most relevant 20 parts or substantially the whole structure of said assembly composed of the support structure, the magnetic field source, and the magnetic field sensing pick-ups. This construction configuration has the advantage of reducing the size of the device, thanks to 25 the removal of the casing 16 as shown in Figure 1 and of avoiding the use of foamed tunnels 12 and 14, which is desirable in apparatuses designed for examinations on human beings. Also, the temperature of the susceptometer may be stabilized thanks to a feedback 30 control of the fluid around it. Magnet temperature is

itself measured with a high sensitivity, and controlled by a feedback system, which modulates the temperature of water flowing through the hollow copper conductors that form magnets.

5 In one embodiment of the invention, as shown in Figs. 8 to 15, to be intended as an alternative to the embodiment of Fig. 1, and particularly adapted to examinations on human beings, the susceptometer has a support structure 20, including an upright 21 with
10 three vertically aligned cantilevers 22 which project on the same side and support the two magnetic field sensing pick-ups and the magnetic field source respectively, in the above specified order, i.e. with the magnetic field source between the two magnetic
15 field sensing pick-ups.

The upright 20 has the shape of a hollow panel or rectangular beam as is apparent from the vertical cross section of Fig. 10 and from the top plan view of Fig. 11.

20 The cantilevers 22 are themselves provided as hollow panels adapted to receive the pickups and the magnetic field source respectively, not shown in detail in Figures 8 to 11. At the end attached to the upright 21, the panels have fastening tabs 122, which are
25 provided as extensions of the vertical side walls, abutting against the corresponding opposite sides of the upright 21. The tabs are fastened with the help of dowels and fast pins, which are denoted as 23 and 24 respectively.

30 A trapezoidal base member 25 for each side wall of

the upright 21 acts as a reinforced fastener between said upright 21 and a base plate 26.

As is apparent from Figure 9, holes 222 and 322 are formed at the end sides of the cantilevers 22, for 5 the insertion of dowels, and fast pins respectively, to secure the magnetic field source and of the pick-ups in the corresponding cantilever.

The structure 20 is made of a non-magnetic material, for instance plastic or fiber-reinforced 10 resin, for instance glass reinforced plastics.

Therefore, the structure 20 has a vertical comb shape.

Referring now to Figure 12, said structure 21 with its pick-ups and the magnetic field source and possibly 15 with sensors and leads for connection with other required construction members are housed in a first inner shell 30 having a corresponding shape and in another outer shell 31, also having a corresponding shape, but such a size as to form a gap for the flow of 20 the above generally described diathermic liquid between the inner shell 30 and the outer shell 31, which are joined together at the rear side and at the base plate to form a gap which is liquid-tight towards the outside of the outer shell 31 and the inside of the 25 inner shell 30. Obviously, the gap communicates with a diathermic fluid feed and drain line through inlets and outlets not shown in detail.

As is apparent from Fig. 12, the two casings with different sizes have a portion 130, 131 which is 30 adapted to receive the upright 21 and cavities 230, 231

for receiving the cantilevers 22. The cavities 230, 231 communicate with the cavities 130, 131 of the upright 21 of the support structure 20, whereas the latter increases in width as it gets closer to the bottom 5 portion, as a trapezium, to form the housing cavity of the trapezoidal base of the support structure. Advantageously this cavity of the trapezoidal base provides a better stability to the structure and other support members 32 may be associated thereto, such as 10 side cross members which, if designed with a tubular shape, may also form inlets and outlets for the diathermic flow, besides improving themselves stability of the whole structure.

The distance between the central magnetic field 15 source and the two pick-ups disposed on opposite sides of the magnetic field source, i.e. between the corresponding cantilevers 22 is such as to allow the introduction of the patient body or a patient table or stretcher between said magnetic field source and one of 20 the two opposite pick-ups.

Advantageously, the stretcher is fitted on a frame that may be lifted and lowered to allow vertical motion of the supporting surface of the table or stretcher, until it reaches the height whereat the stretcher with 25 the patient body on it may be introduced either in the space between the upper pick-up and the intermediate magnetic field source or in the space between said intermediate field and the lower pick-up. At the junction with the cantilevers, the stretcher may have a 30 recess, whose size and shape substantially correspond

to those of the cantilevers or an aperture coinciding with the body part to be screened, typically the liver.

Figs. 13 to 15 show a patient table combined with the inventive susceptometer. The table 40 is shown in 5 Figs. 13 and 14 in its two operating positions. The table structure is composed of a surface for supporting the body under examination, possibly having a recess whose shape is complementary to the cantilever shape, and in which either the cantilever with the lower pick-10 up (Fig. 13) or the one with the magnetic field source (Fig. 14) may penetrate, in the operating condition, to carry the body part to be screened in the proper position, in line with the pick-ups and with the magnetic field source.

15 It shall be noted that the patient does not need to be moved relative to the stretcher or table 40, and always keeps its position through the two or more different measuring steps, thereby simplifying data analysis.

20 It shall also be noted that the same patient turns his/her back or abdomen to the magnetic field source depending on his/her insertion in the space above or below the magnetic field source. In these conditions, several measurements may be made, particularly at least 25 two measurements, each with a different patient orientation with respect to the three magnetic field sources, hence the three magnetic fields generated thereby. Also, when two different magnetic field measuring pick-ups are used (Fig. 16), 12 measurements 30 may be made for each patient position relative to the

magnetic field axis, and this allows for a simpler determination of excess iron stores in the body and of the distribution thereof.

With reference to the embodiment as shown in Figures 13 to 15, the table or stretcher is supported by a member composed of jointed arms, which allows the table or stretcher to be positioned at different heights.

In the embodiment as shown in Figures 13 to 15, the lower ends of four lifting arms 42 are jointed to a base of the table 40 which acts as a trolley 41. An arm 42 is provided on each transverse side of the table, and is jointed at its ends to the base 41 and to the body supporting surface 40 respectively. The axes of articulation of the two arms 42 are coincident. A second arm 42' for each jointed arm 42 is, in turn jointed to the base 41, but it is free to run to the upper end toward the plane defined by the arm 42' and passes through an aperture 142 of the arm 42. Abutment means are provided along the arm 42, which engage with the edges of the aperture 142 and allow the surface to be locked in position, preventing the table to be lowered unless it is previously released by a slight lifting action. These systems are well-known and any surface lifting and lowering arrangement may be used.

The base 41 and the patient supporting surface 43 overhang from the structure side 20, that carries the magnetic field source 2 and the pick-ups 4, 6, the arm system 42, 42', being eccentric with respect to said two surfaces.

Nevertheless, in combination with the means for lifting and/or lowering the body supporting surface (43), removable means are provided for locking this body supporting surface (43) in position.

5 It shall be noted that all the structural support members of the apparatus and table, as well as the shells that form the susceptometer case are made of a non-magnetic material, particularly glass-reinforced plastics or the like.

10 A further embodiment of the magnetic field source and the pick-ups is shown in Figure 16. In this embodiment two magnetic field sources 2 and 2' are provided, having different extensions, and hence being able to generate magnetic fluxes in a larger volume and 15 in a smaller volume. In this case, two pick-ups 4, 4' and 6, 6' are provided on each side of the two magnetic field sources 2, 2', and in line therewith, to sense the magnetic fields generated by the larger source 2 and by the smaller source 2'.

20 Here, the two sources 2, 2' are made of two circular annular superconducting coils, with hollow copper conductors, which are coaxial and concentric. Similarly, the pick-ups 4, 4' and 6, 6' of the two pairs of pick-ups are made of coaxial and concentric 25 circular annular coils, whose positions are axially coincident with the corresponding magnetic field generating coil for said two sources 2, 2'. In order to minimize the stray capacity of pick-ups, the latter are formed of several superposed printed circuit layers.

30 An additional magnet may be positioned coaxially

inside the inner pickups 4' and 6'.

Thanks to the three magnetic field sources and to the concentric pick-ups, 12 measurements may be made, as mentioned above, for each patient position relative 5 to the magnetic field axis, and this allows for a simpler determination of excess iron stores in the body and of the distribution thereof.

This invention shall not be intended to be limited to the embodiments described and illustrated herein, 10 which are to be considered as implementation examples only; the invention is subject to modification, as regards shape, arrangement of parts, construction details and operation. For instance, the possibility of providing several magnetic field geometries might 15 suggest the attempt to design a geometry in which the inner product ($B \cdot b$) is distributed with a relatively high gradient in the heart region, and in which the magnetic properties of this organ might be obtained by synchronizing magnetic signal detection with heart 20 beats.

CLAIMS

1. A susceptometer for non-invasive determination of iron concentration in a body, by detecting the magnetic flux variation produced by the body,
5 characterized in that it comprises:
 - a heat insulating case (16), containing a support structure, which is made of a non-magnetic and electrically insulating material, and operationally kept substantially at room temperature, and which
 - 10 defines a screening region (8, 10);
 - an alternating magnetic field source (2), supported by said structure and able to generate a magnetic field in said screening region;
 - at least two magnetic field sensors (4, 6),
15 supported by said structure and disposed in front of said field source (2);
 - means (12, 14) for introducing the body to be screened in the screening region (8, 10) defined by said field source (2) and at least one of said at least two sensors (4, 6);
 - temperature control means, for stabilizing temperature inside said case, at least during measurement, in such a manner as to limit relative variation to a predetermined maximum value, so that
 - 20 25 thermal expansion of the support structure and the associated field source (2) and sensors (4, 6) are substantially ininfluent on the variations in the magnetic field flux linked with the sensors (4, 6); and
 - means for processing electric signals indicative of the variation in the magnetic flux linked with the



sensor, which variation is caused by the presence of the body being screened, in the screening region.

2. A susceptometer as claimed in claim 1, characterized in that it has a first (4) and a second 5 (6) sensors, which are arranged on the support structure in symmetrical positions with respect to said field source (2) and wherein a screening region (8, 10) is defined between said field source (2) and each sensor (4, 6).

10 3. A susceptometer as claimed in one or more of the preceding claims, characterized in that it further includes at least two additional sensors (20, 22), which are supported by said structure and arranged in the proximity of the field source (2) in front of it, 15 so that the variation of the magnetic field flux linked with said additional sensors, which is caused by the presence of a body in this screening region, is substantially the effect of the magnetic properties of the outermost parts of said body.

20 4. A susceptometer as claimed in one or more of the preceding claims 1 to 3, characterized in that it has a second heat insulating case (18), which defines a temperature controlled environment in it.

25 5. A susceptometer as claimed in claim 4, characterized in that said means for introducing the body to be screened include a first (12) and a second (14) tunnels, made of a non-magnetic insulating material, and disposed in the screening regions (8, 10) respectively, with an introduction aperture outside the 30 walls of said first (12) and second (18) cases.

6. A susceptometer as claimed in one or more of the preceding claims, characterized in that said temperature control means comprise a plurality of heating/cooling members, associated to the support 5 structure, temperature sensing means for detecting temperature near said heating/cooling means and means for adjusting the temperature of said heating/cooling means, as a function of the temperature measured by said sensors.

10 7. A susceptometer as claimed in claim 6, characterized in that said heating/cooling means have weak magnetic properties.

15 8. A susceptometer as claimed in one or more of the preceding claims 1 to 5, characterized in that said temperature control means include heating/cooling means associated to the walls of said first case (16) and/or said second case (18).

20 9. A susceptometer as claimed in claim 5, characterized in that said temperature control means include heating/cooling means associated to the walls of said first (12) and second (14) tunnels.

25 10. A susceptometer as claimed in one or more of the preceding claims 1 to 9, characterized in that said processing means include a lock-in amplifier, which is able to read the signal produced by said sensors, wherein the signal read by said lock-in amplifier is null if no sample is inserted in said screening region.

30 11. A susceptometer as claimed in claim 10, characterized in that the processing means include a computer, which is arranged to acquire the output

signal of said lock-in amplifier in synchronism with the introduction and extraction of the sample from the screening region.

12. A susceptometer as claimed in one or more of 5 the preceding claims, characterized in that the first case (16, 18; 30, 31) and the second case define a liquid-tight gap therebetween, through which a temperature-controlled diathermic fluid flows, to stabilize the temperature of the susceptometer 10 structure.

13. A susceptometer as claimed in one or more of the preceding claims, characterized in that it has a support structure for the magnetic field source/s (2, 2' and small magnet) and the pick-ups (4, 4'; 6, 6'), 15 including an upright (21), wherefrom three cantilevers (22) project at different heights and in substantially aligned positions to support the magnetic field source/s (2, 2' and small magnet) and the pick-up/s (4, 4'; 6, 6') respectively.

20 14. A susceptometer as claimed in claim 13, characterized in that the upright (21) and/or the cantilevers (22) are provided as tubular or box-like elements, like panels, and may be removably fastened together by locking and/or centering means.

25 15. A susceptometer as claimed in claim 12 or 13, characterized in that the cantilevers (22) are joined to the upright by means of extensions of their vertical side walls, which have the form of fastening tabs, abutting against the corresponding side walls of the 30 upright (21) and secured thereto by means of fast pins

and dowels (23, 24).

16. A susceptometer as claimed in one or more of the preceding claims 12 to 15, characterized in that the cantilevers (22) have cavities for receiving the 5 pick-up/s (4, 4'; 6, 6') and the magnetic field source/s (2, 2' and small magnet) respectively, which cavities are formed within the thickness of said cantilevers.

17. A susceptometer as claimed in one or more of 10 the preceding claims 12 to 16, characterized in that the pick-up/s and the magnetic field source/s are secured inside the thickness of the cantilevers (22) by dowels (222) and fast pins (322).

18. A susceptometer as claimed in one or more of 15 the preceding claims 12 to 17, characterized in that the lower end upon which the upright rests, is connected to a base plate by means of trapezoidal reinforcement plates (25), which are fastened to said base (26) and to the side walls of the upright (21)

20 19. A susceptometer as claimed in one or more of the preceding claims 12 to 18, characterized in that the support structure (20) with the pick-ups (4, 4'; 6, 6') and with the magnetic field source/s (2, 2' and small magnet) are accommodated in a first inner shell 25 (30), which has a cavity (130) for housing the upright (21) which cavity communicates with three cavities for housing the cantilevers (22), the lower portion of the first cavity (130) being widened to form a trapezium which corresponds to the trapezoid base (25) of the 30 support structure (20).

20. A susceptometer as claimed in claim 19, characterized in that the assembly composed of the support structure (20) with the pick-ups (4, 4'; 6, 6') and with the magnetic field source/s (2, 2' and small magnet) and its first inner shell (30) are accommodated in a second outer shell (31), whose shape corresponds to that of the first inner shell (30), and whose size is larger to form a sealable gap, through which a diathermic fluid may flow for temperature stabilization purposes.

10 21. A susceptometer as claimed in one of claims 19 or 20, characterized in that the first inner shell has two tubular supporting beams (32) along the side walls, at the trapezoidal widened base.

15 22. A susceptometer as claimed in claim 21, characterized in that the two tubular support beams (32) also act as inlets and outlets for the diathermic fluid flowing in the gap between the inner shell (30) and the outer shell (31).

20 23. A susceptometer as claimed in one or more of the preceding claims 12 to 22, characterized in that it is provided in combination with a patient table, a stretcher, or the like (40), whose patient supporting surface (43) is supported in such a manner as to be 25 able to move vertically between the two operating positions in which the body to be screened is introduced, between the cantilever that supports the magnets (2, 2') and the cantilever of upper pick-ups (4, 4') and between the cantilever that supports the 30 magnets (2, 2') and the cantilever (22) of lower pick-

ups (6, 6') respectively.

24. A susceptometer as claimed in claim 23, characterized in that the patient supporting surface has a cavity for accommodating the cantilever (22) that 5 supports the lower pick-up/s (6, 6') and/or the cantilever (22) that supports the magnetic field source/s (2, 2').

25. A susceptometer as claimed in claim 23 or 24, characterized in that the patient table or stretcher 10 (40) has a base (41) that runs on rails.

26. A susceptometer as claimed in one or more of claims 23 to 25, characterized in that the body supporting surface (43) may be lifted or lowered with respect to the base (41), thanks to a jointed arm 15 lifting system (42) and removable position lock means.

27. A susceptometer as claimed in one or more of the preceding claims, characterized in that it has three magnetic field sources (2, 2' and small magnet), each being able to generate different magnetic field 20 flux distributions.

28. A susceptometer as claimed in claim 27, characterized in that two pick-ups (4, 4'; 6, 6') are provided on each side of the magnetic field sources (2, 2'), each being dimensionally adapted to the volume 25 permeated by the magnetic flux of the corresponding magnetic field source (2, 2').

29. A susceptometer as claimed in one or more of the preceding claims 28 to 28, characterized in that it has two magnetic field sources (2, 2'), formed by 30 annular circular coils, which have different diameters,

one being contained in the other, and are coaxial to each other and to the two pick-ups (4, 4'; 6, 6'), the latter being themselves provided as coils, one in the other and coaxial to each other, the size of concentric 5 coils (4, 4'; 6, 6') being adapted to the size of the corresponding magnetic field source (2, 2').

30. A susceptometer as claimed in one or more of the preceding claims, characterized in that an additional magnetic field source is associated to each 10 pick-up or pick-up pair (4, 4'; 6, 6').

31. A susceptometer as claimed in claim 30, characterized in that said magnetic field source has an annular shape and is mounted coaxially inside the smaller pick-up of each pick-up pair (4, 4'; 6, 6').

15 32. A method for measuring the content of magnetic material, particularly metals, especially iron, in a body, by a susceptometric measurement of field variations caused by the presence of said screened body in the magnetic flux, which includes the steps of:

20 a) generating a measuring magnetic field;
b) measuring the magnetic field that permeates the screened body;
c) measuring the magnetic field with no body in it, for generating a reference signal;

25 d) comparing the reference signal with the measuring signal, obtained with a body in the magnetic flux; the magnetic material build-up in the screened body is derived from the difference between said two signals.

30 characterized in that the reference signal and the

actual body signal are measured at the same time, by generating a magnetic field that is symmetric with respect to a magnetic field source, the reference signal being measured on one side of the magnetic field source and the actual body signal being measured on the opposite side of the magnetic field source, whereas the build up of magnetic material in the body being screened is derived from the difference between said two signals.

10 33. A method as claimed in claim 32, characterized in that said measurements are also made by inverting the position of the screened body with respect to the magnetic field source.

15 34. A method as claimed in claim 32 or 33, characterized in that several measurements are made for each measuring configuration.

20 35. A method as claimed in one or more of the preceding claims 32 to 34, characterized in that the structure for supporting the magnetic field source and the field measuring means is kept at a constant temperature, during measuring operations.

25 36. A method as claimed in one or more of the preceding claims 32 to 35, characterized in that magnetic fields are generated for each measurement, which have a different spatial extension, and permeate wider or narrower portions of the screened body respectively.

30 37. A method as claimed in claim 36, characterized in that said magnetic fields having different spatial extensions are coaxial to each other.

38. A method as claimed in claim 36 or 37, characterized in that it all measurements of the process are used to determine iron overload in the human body and the distribution thereof.

5 39. A method as claimed in one or more of the preceding claims 32 to 38, for determining the amount of iron stores in the liver.

10 40. A method as claimed in claim 39, for in vivo determination of the amount of iron stores in the liver.

41. A method as claimed in claim 40, for determination of the amount of iron stores in the liver of thalassemic patients.

101538411

WO 2004/055515

PCT/EP2002/014251

1/9

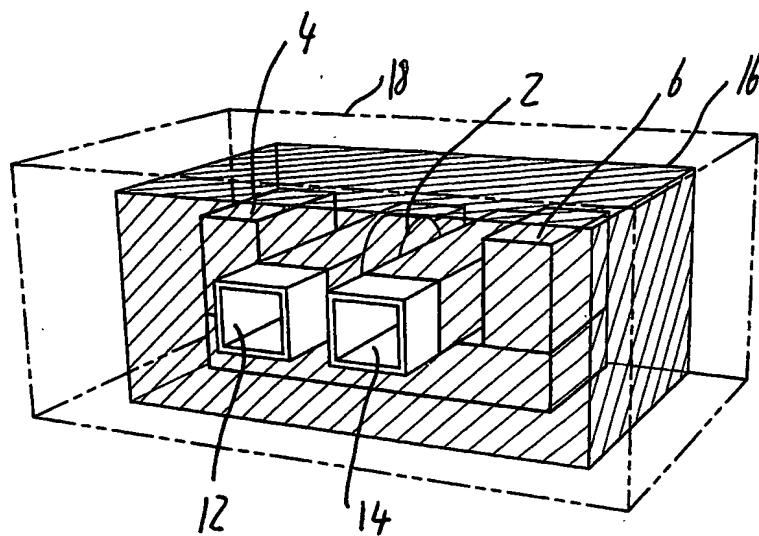


Fig. 1

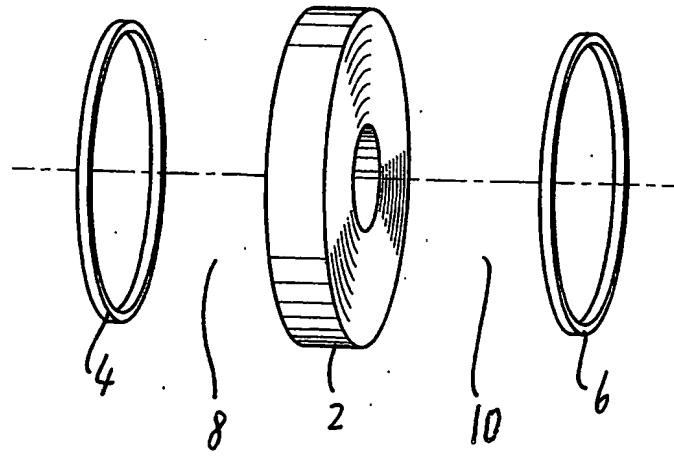
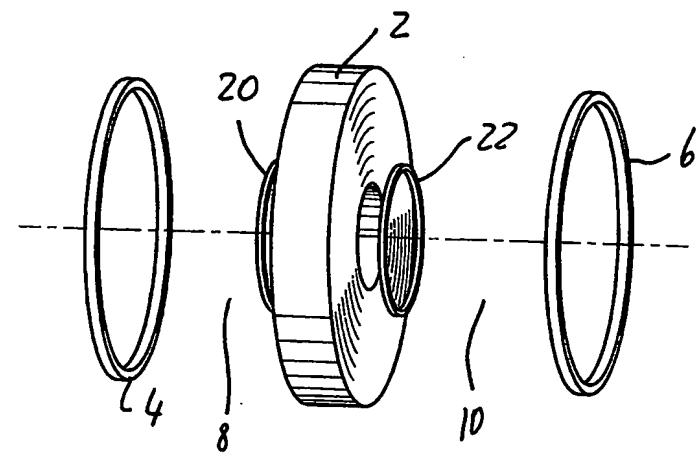
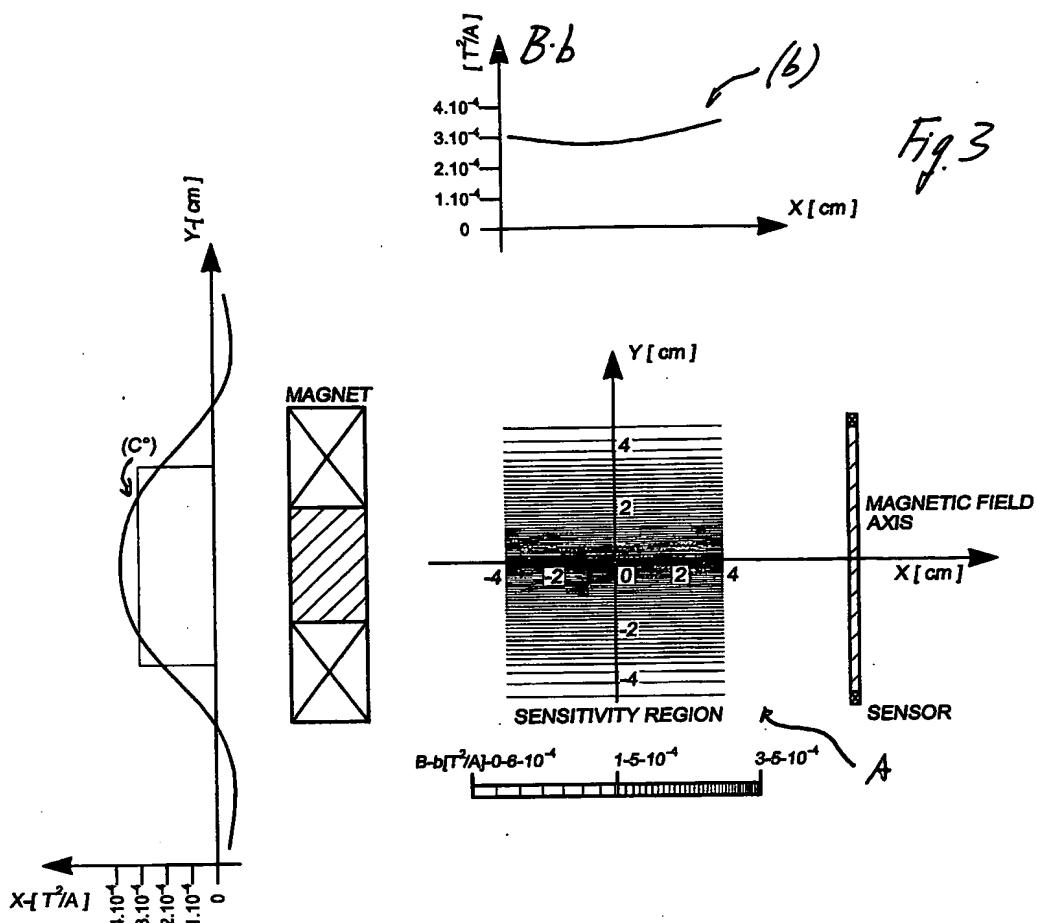


Fig. 2

SUBSTITUTE SHEET (RULE 26)



SIGNAL OF A CYLINDRICAL 170cc WATER SAMPLE

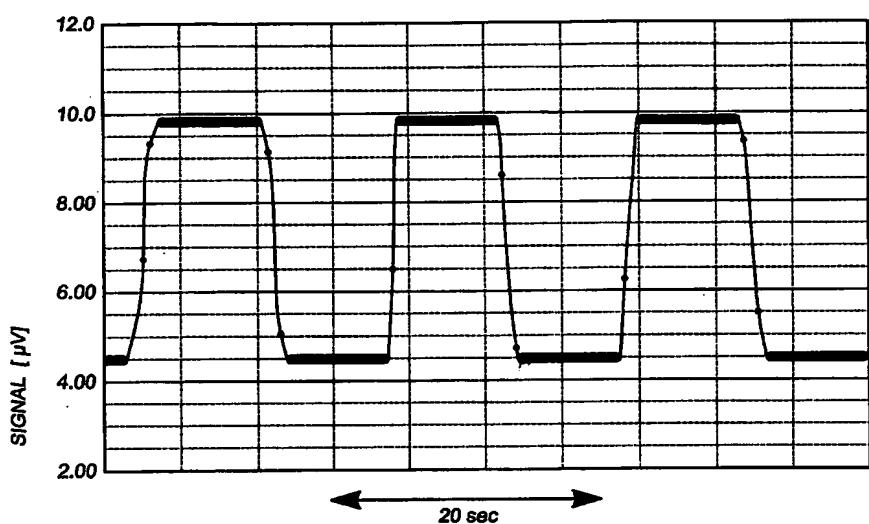


Fig. 4

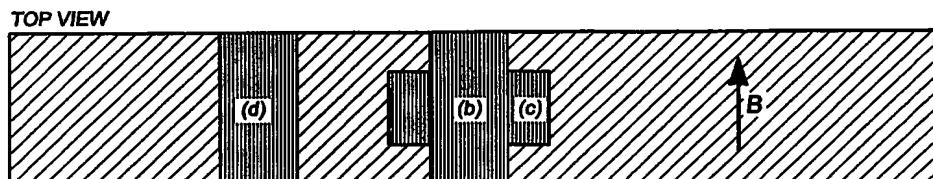
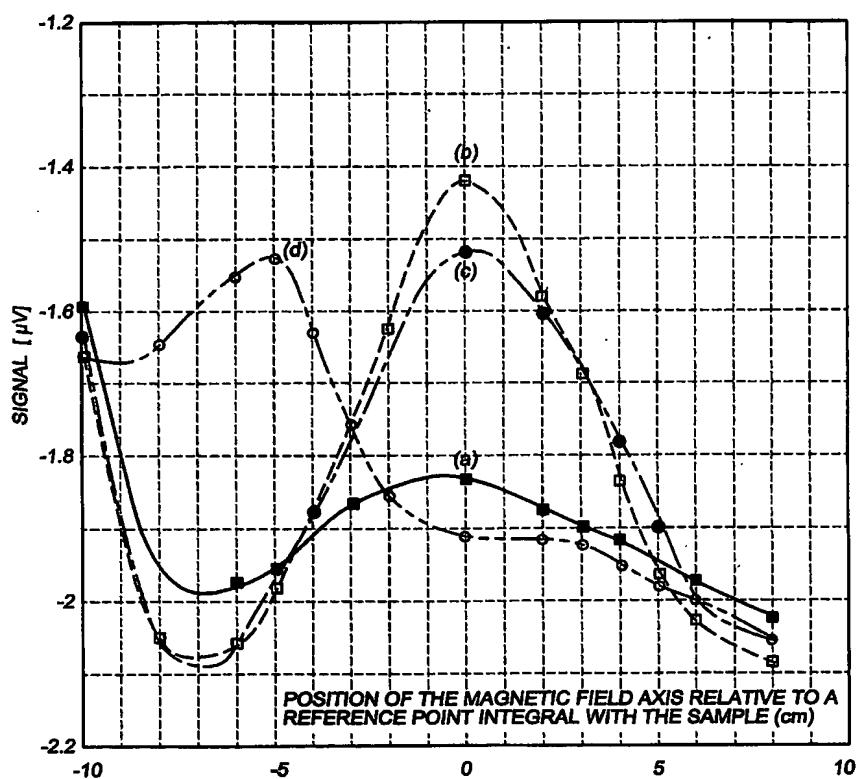
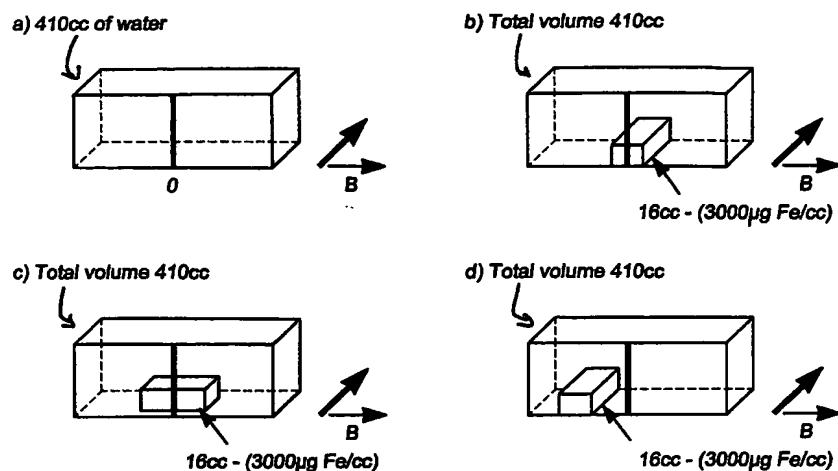


Fig. 5

SUBSTITUTE SHEET (RULE 26)

COMPARISON OF SIGNALS OBTAINED
WITH DIFFERENT GEOMETRIES

16,5 cc solution

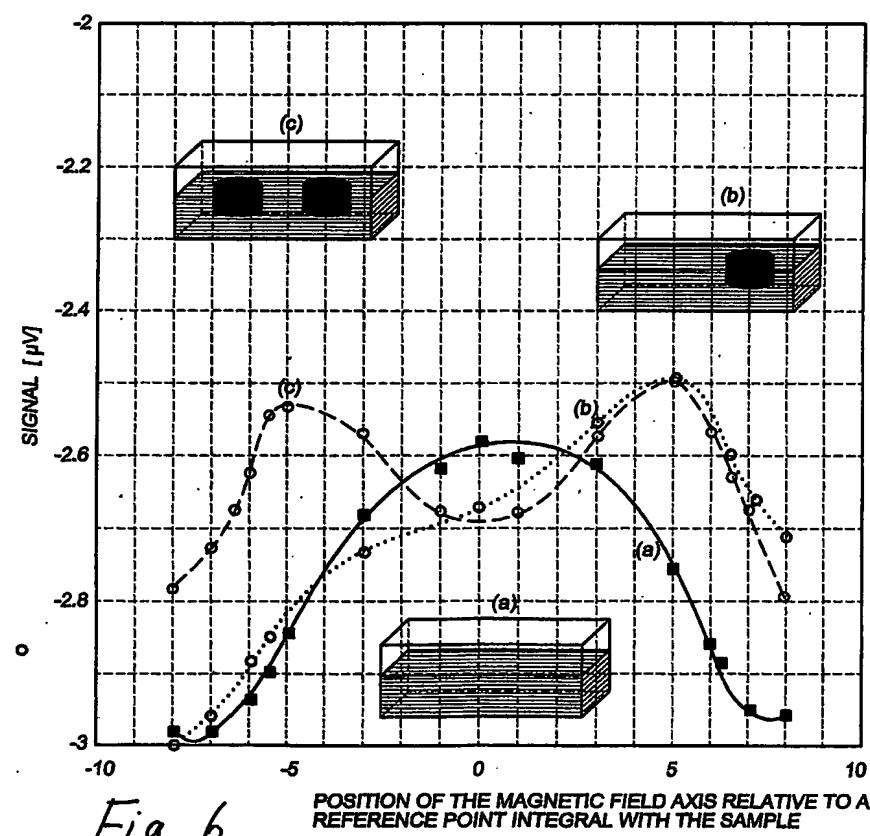
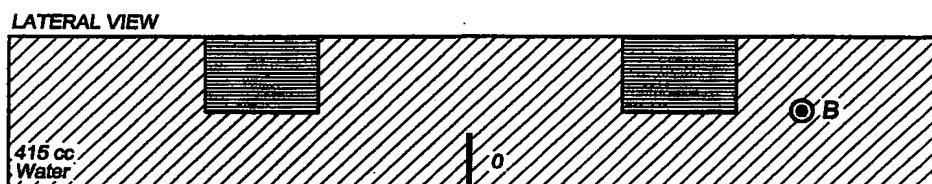
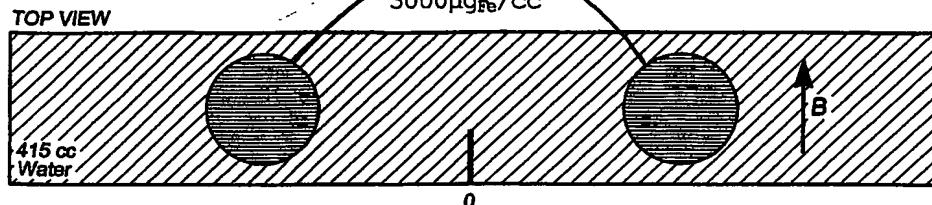
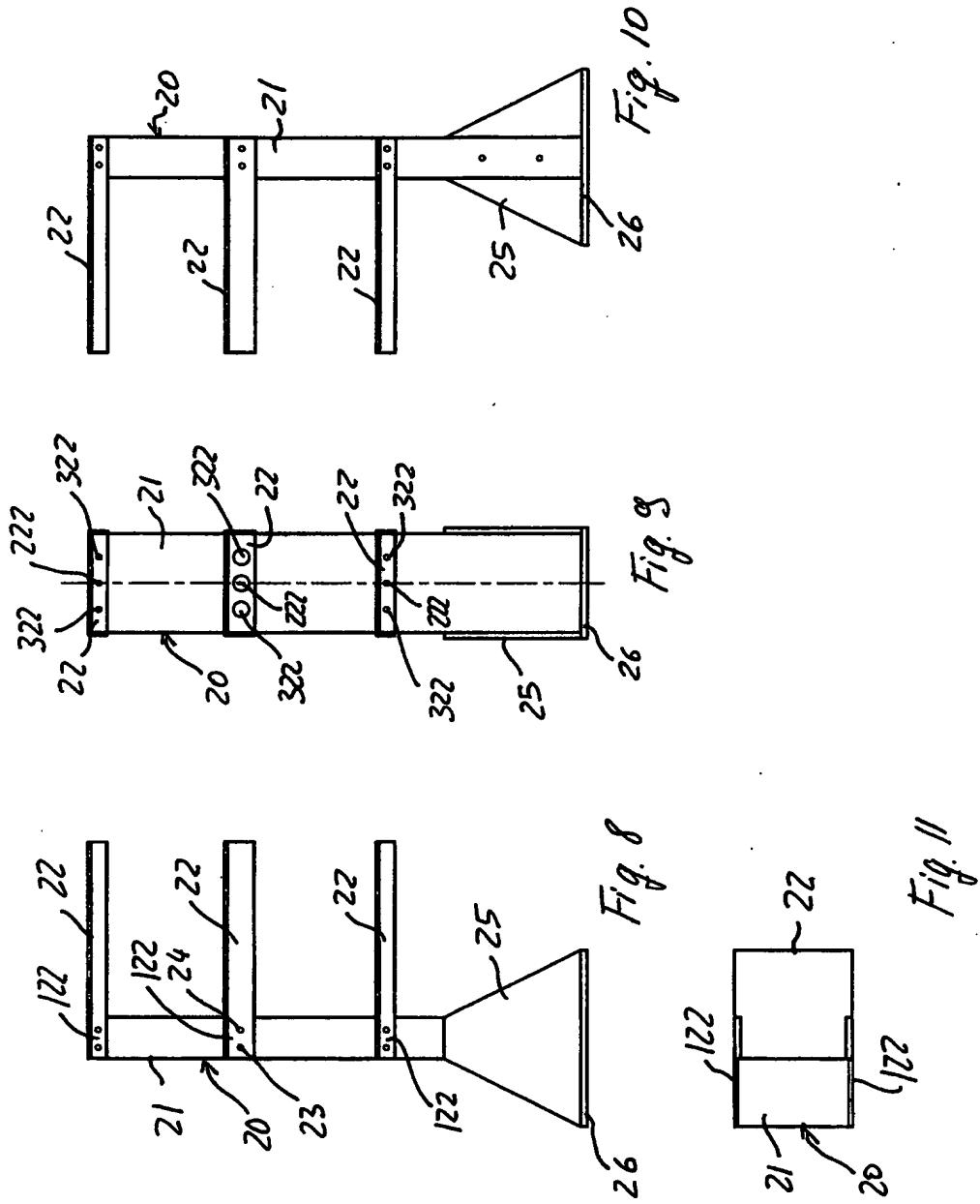
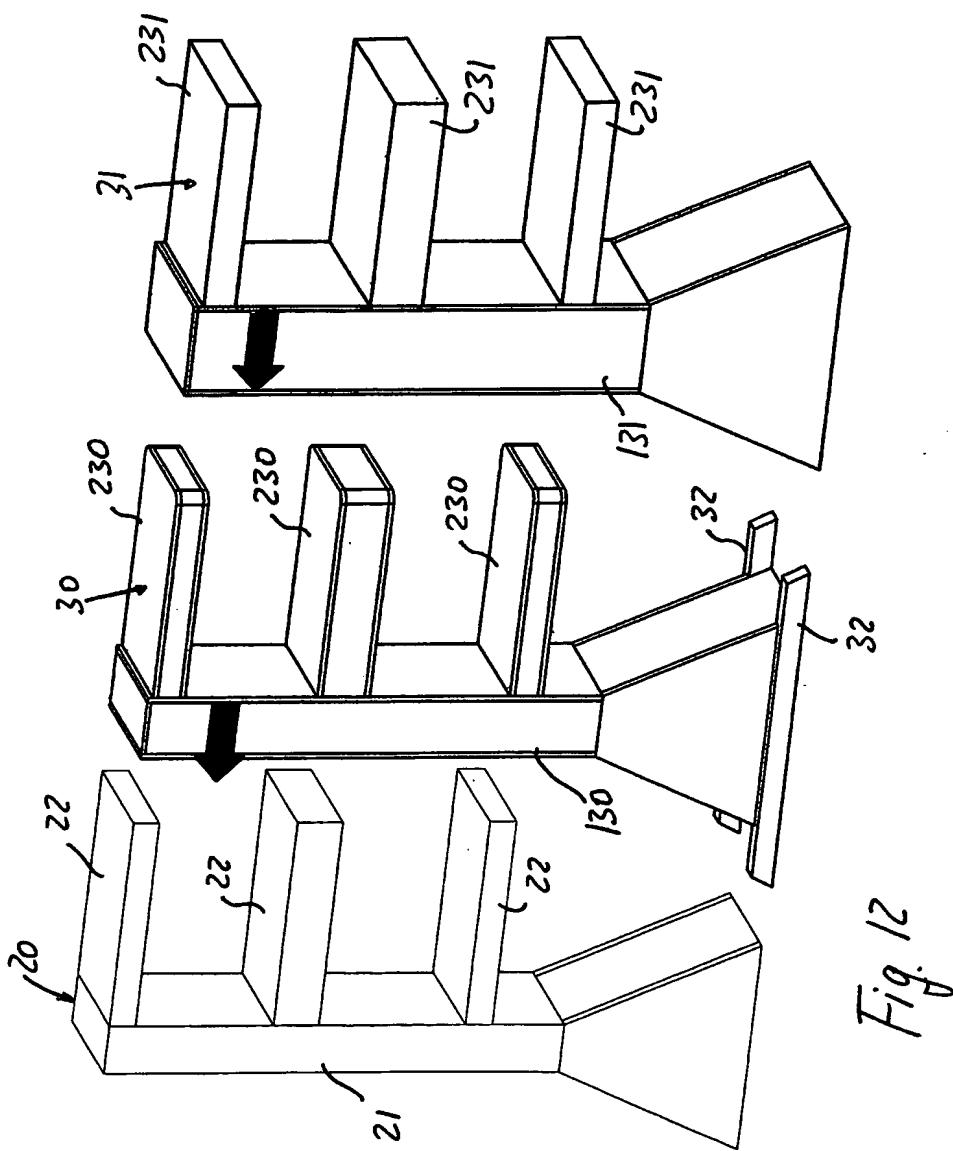
3000 $\mu\text{g}_{\text{Fe}}/\text{cc}$ 

Fig. 6





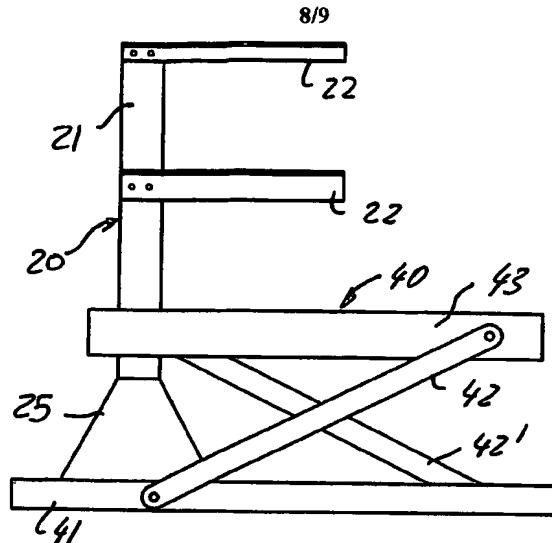


Fig. 13

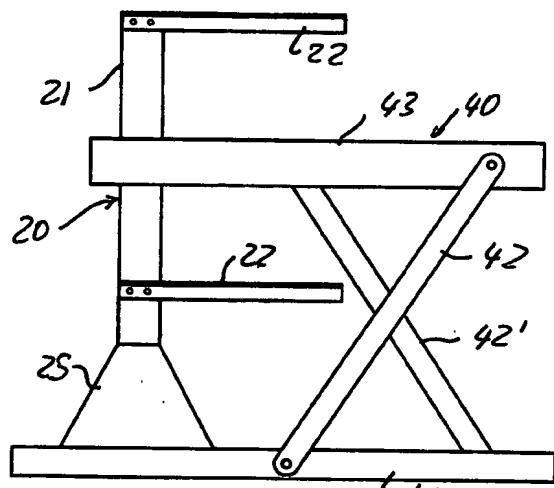


Fig. 14

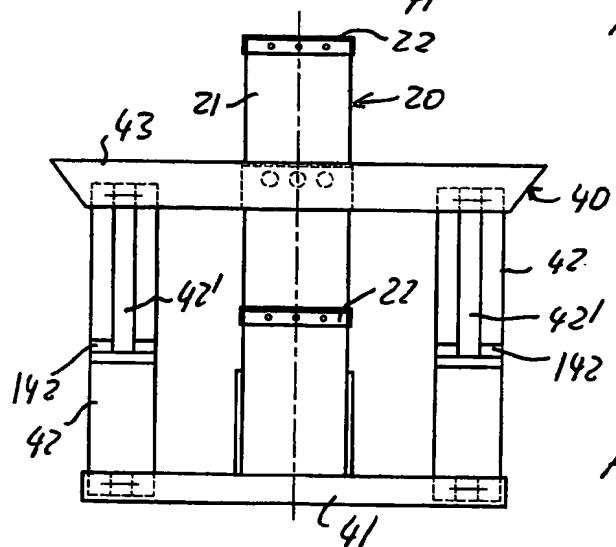


Fig. 15

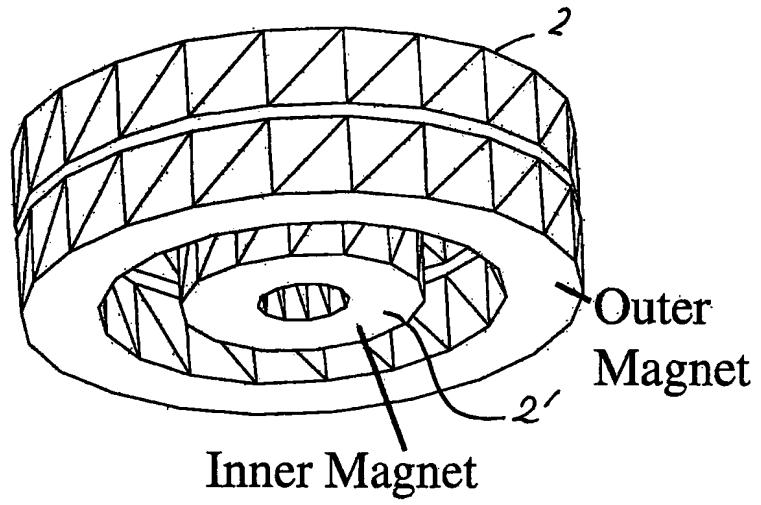
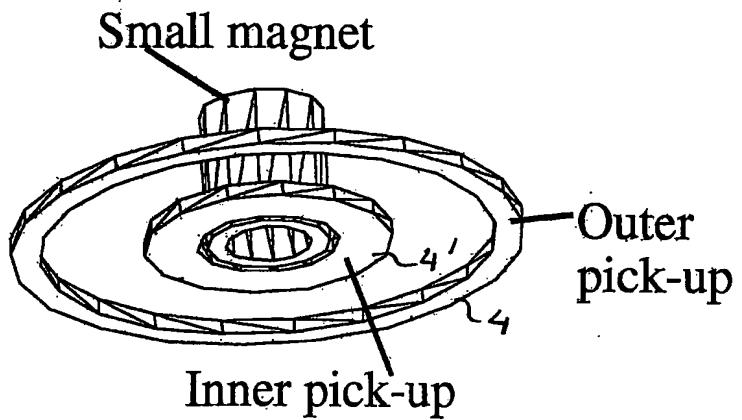
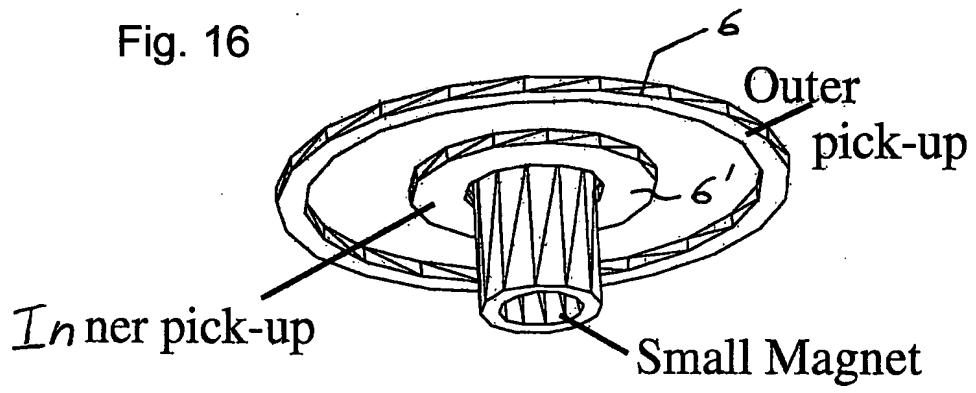


Fig. 16



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14251

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/49 G01N33/487 G01N27/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JOHN H. BAUMAN, RICHARD W. HOFFMAN: "Magnetic Susceptibility Meter for In Vivo Estimation of Hepatic Iron Stores" TRANSACTIONS ON BIO-MEDICAL ENGINEERING, vol. 14, no. 4, October 1967 (1967-10), pages 239-243, XP001150027 cited in the application abstract page 241, left-hand column, paragraph 3 -page 242, left-hand column, paragraph 2; figures 2,3</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-41

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

20 August 2003

Date of mailing of the International search report

29/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kempf, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14251

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. STEKETEE, H. ROGGEVEEN, Y.J. KINGMA: "Measurement of magnetic susceptibility in living rats" MEIDCAL & BIOLOGICAL ENGINEERING & COMPUTING, vol. 18, 1980, pages 253-260, XP001150020 cited in the application abstract page 254, right-hand column, paragraph 1 -page 256, left-hand column, paragraph 1; figures 2-5	1-41
A	WO 01 40790 A (QUANTUM DESIGN INC) 7 June 2001 (2001-06-07) abstract page 12, line 1 -page 13, line 7; figure 4	1-41
A	US 2001/011155 A1 (RAPOPORT) 2 August 2001 (2001-08-02) abstract page 2, right-hand column, paragraph 8 -page 3, right-hand column, paragraph 1; figure 1	1-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP 02/14251

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0140790	A	07-06-2001	US	6437563 B1	20-08-2002
			AU	3272901 A	12-06-2001
			CA	2394857 A1	07-06-2001
			CN	1402833 T	12-03-2003
			EP	1240509 A1	18-09-2002
			JP	2003515743 T	07-05-2003
			WO	0140790 A1	07-06-2001
			US	2001052769 A1	20-12-2001
			US	2001052770 A1	20-12-2001
US 2001011155	A1	02-08-2001	US	5978694 A	02-11-1999
			AU	2869900 A	25-08-2000
			WO	0045697 A1	10-08-2000
			AU	728256 B2	04-01-2001
			AU	6341898 A	18-09-1998
			BR	9808650 A	23-05-2000
			CN	1249672 T	05-04-2000
			EP	0964640 A1	22-12-1999
			JP	2002510988 T	09-04-2002
			TW	434412 B	16-05-2001
			WO	9837808 A1	03-09-1998